REMARKS/ARGUMENTS

Claim 1 has been amended by rearrangement of elements explicitly or inherently present in the claim as originally filed and without altering the scope of the claims. For example, the introduction of the phrase "the presence of" in the preamble simply makes explicit the implicit correspondence between the preamble and the last clause of the claim.

The phrase "attached to a detectable nucleic acid molecule" is simply a re-phrasing and relocation of the original phrase "wherein said agent is attached to a detectable nucleic acid molecule". The original phrase clearly provides support for the language. Both the original and amended phrase clearly refer to a feature of the same "agent" as recited in the claim. No change in scope of "agent" or the claim has occurred with the amendment. Further discussion of this amendment is provided below.

The phrase "which agent binds said ligand" is simply a re-phrasing of the original phrase "capable of binding said ligand" as suggested in the Office Action mailed 1 June 2004. The original phrase clearly provides support for the language. Again, both the original and amended phrase clearly refer to the functionality of the same "agent" as recited in the claim. No change in scope of "agent" or the claim has occurred with the amendment. Further discussion of this amendment is provided below.

New claim 21 is supported at least on page 9, second paragraph.

No new matter has been introduced, and entry of the amendments is respectfully requested.

Telephonic Interview of 12 August 2004

Applicants wish to express their thanks to Examiners Chunduru and Jehanne Sitton for their courtesy and helpfulness during a telephonic interview on 12 August 2004 with the undersigned.

During the interview, the Examiners noted with approval a proposed amendment to recite the phrase "the presence of" in the preamble of claim 1 because the amendment simply reflects subject matter already present in the claimed invention by virtue of the last clause.

The interview also included a discussion regarding the interpretation of the scope of claim 1. Applicants pointed out that contrary to the interpretation of the claim as presented on page 3 of the Office Action mailed 1 June 2004, the scope of the claim does not encompass methods wherein the ligand to be detected was the same as the detectable nucleic acid.

Applicants pointed out that the agent used to bind the ligand was explicitly identified in the claim as being attached to a detectable nucleic acid which is distinct from the ligand to be bound by the agent. In fact, the claim utilizes three distinct terms for three separate entities: "ligand" for the ligand to be detected by the claim methods; "agent" for the entity which binds the ligand; and "detectable nucleic acid molecule" for the reporter moiety attached to the agent. Moreover, a review of the claim in light of the specification shows that the claims and the invention as disclosed are directed to "immuno-PCR" like methods wherein the detection of a ligand of interest is performed *indirectly* by detection of a detectable nucleic acid molecule. Accordingly, the ligand and the detectable nucleic acid molecule are distinct entities in the claimed methods.

Examiner Sitton noted that a rearrangement of the language in claim 1, which originally recited that the detectable nucleic acid molecule "is attached" to the agent, would likely resolve the differences in claim interpretation. Applicants thank Examiner Sitton for the suggestion, which has been adopted as presented above without altering the attachment of the nucleic acid molecule to the agent or the scope of the claims.

The interview also included a discussion of the phrase "capable of binding" as presented in claim 1. This phrase has been revised as presented above and explained below.

Claim Rejections under 35 USC § 112, second paragraph

Claims 1-20 were rejected under 35 USC § 112, second paragraph as allegedly indefinite for reciting "capable of binding" in claim 1 because "capability is a latent characteristic and the claims do not set forth the criteria by which to determine capability." The

statement of the rejection includes a suggestion to obviate this rejection by revising the language to be "which binds".

Applicants have carefully reviewed the instant rejection and respectfully traverse because no *prima facie* case of indefiniteness has been set forth. A skilled person in the relevant art would understand that "capable of binding" does not encompass the use of an agent that cannot bind the ligand to be detected. As evident from the plain language and the disclosure of the claimed invention, the agent must have the ability to bind the ligand for the claimed methods to function as claimed. Applicants respectfully submit that contrary to the statement of the rejection, there is no requirement in U.S. patent law for the claims to define how to determine the "capability of binding" because the claims simply set out the scope of using an agent having the ability to bind the ligand. That ability is immediately evident upon detection of the nucleic acid molecule as part of the methods encompassed by claim 1. Accordingly, no case of indefiniteness has been presented.

The phrase "capable of binding" was chosen to improve clarity and reduce ambiguity by preventing the possible interpretation that the agent must bind under all possible conditions under which the claimed methods could be used. Another unwarranted interpretation is where the agent must remain bound to the ligand. No such scope was or is intended because, as would be clear to the skilled person, there are conditions under which any method is inoperable and there is no requirement for the agent to remain irreversibly bound.

Given the express suggestion in the statement of the rejection to affirmatively recite the "which binds" phrase, the Examiner has apparently recognized that the claims do not require the agent to bind under all possible conditions. Accordingly, claim 1 has been revised as suggested and without altering the scope of the invention being claimed for the reasons provided above.

Applicants thus submit that this rejection may be properly withdrawn for the reasons provided above.

Claims 1-20 were rejected under 35 USC § 112, second paragraph as allegedly indefinite because "claim 1 recites detecting a ligand in the preamble of the claim and in the last step of the claim recites detecting said nucleic acid."

Applicants have carefully reviewed the instant rejection and believe that it is related to the erroneous interpretation, as discussed above, of the claims as encompassing methods wherein the ligand to be detected and the detectable nucleic acid molecule are the same. Applicants traversal of this interpretation has been provided above. Additionally, the instant rejection appears to not have appreciated the presence of the last clause in claim 1.

Moreover, Applicants respectfully point out that the claims and the invention as disclosed are directed to "immuno-PCR" like methods wherein the detection of a ligand of interest is performed *indirectly* by detection of a detectable nucleic acid molecule. Recognition of this indirect relationship by a skilled person in the relevant art makes the scope of claim 1 clear because the claimed methods do not require a *direct* detection of the ligand.

For the above reasons, no *prima facie* case of indefiniteness has been set forth.

Nevertheless, and in the interest of advancing prosecution, the preamble of claim 1 has been amended to correspond to the language at the end of claim 1 without altering the scope of the claims.

In light of the above, Applicants thus submit that this rejection may be properly withdrawn.

Claim Rejections under 35 USC § 102

As an initial matter, Applicants note that the rejections under this statutory requirement are all based on the interpretation of the claims (see page 3 of the Office Action mailed 1 June 2004) as encompassing methods wherein the ligand to be detected and the detectable nucleic acid molecule "are one and the same". As explained above, this interpretation is inconsistent with the claims and the invention as disclosed, which are directed to "immuno-PCR" like methods wherein the ligand of interest is distinct from the detectable nucleic acid molecule used.

In light of the above amendment to claim 1 and discussion, Applicants believe that the rejections discussed below have all been obviated. Nevertheless, Applicants address each separately and in the order presented.

Claims 1, 3-8, 13-15, and 18-20 were rejected under 35 USC § 102(b) as allegedly anticipated by Erlander et al. (WO 00/28092)

Applicants have carefully reviewed the statement of the instant rejection and respectfully traverse because no *prima facie* case of anticipation is present. Simply put, Erlander et al. do not teach all the requirements of the claims.

As an initial matter, Applicants note that Erlander et al. disclose two types of detection related methods. The first is *in situ* hybridization as described in Example 7 (pages 15-16) and which is distinct from the instant invention. The second is microarray based, as described in Examples 2-6 (pages 11-15) wherein labeled cDNAs prepared from RNA of a sample are hybridized to microarrays comprising probes for the cDNAs. This disclosure in Erlander et al. is also distinct from the instant invention.

Thus, and contrary to the assertion in the statement of the rejection, Erlander et al. do not anticipate the claims because they disclose wholly different methods. For example, and contrary to the statement of the rejection, cited page 3, lines 1-2, and page 15, lines 19-28, from Erlander et al. (directed to *in situ* hybridization methods) do not anticipate the instant claims. Instead, page 15, Example 7, describes the use of RNA probes (produced from cDNAs) that are radiolabeled throughout with ^{35}S labeled uracil bases. The probes are then hybridized to rat DRG sections on slides, which are subsequently exposed to film. Comparing this Example 7 to claim 1, multiple components and actions of claim 1 are missing from Erlander et al. Where is the detectable nucleic acid molecule attached to a binding agent? Where is the act of staining to identify cells of interest? Where is the act of capturing or isolating the cells of interest? In light of these deficiencies, Erlander et al. cannot anticipate the claims.

Page 3, lines 1-2 simply describes *in situ* hybridization using cDNA probes. Again, multiple factors are missing in comparison to the requirements of claim 1.

As noted above, the instant invention is not directed to simple *in situ* hybridization as known in the art or utilized by Erlander et al. Instead, the invention of claim 1 requires specific components and actions which are not disclosed by Erlander et al.

Moreover, and with respect to claims 4, 5, and 18, the cited passages from Erlander et al. (page 4, lines 11-29, and page 5, lines 11-27) do not disclose PCR amplification or PCR-mediated quantitative analysis. Neither of the cited passages even mention PCR. Instead, they relate to the amplification of RNA (see the passage from page 4) without any indication of such amplification being PCR-mediated. The passage from page 5 deals with the identification of expressed mRNAs as well as their *relative* and *qualitative* levels of expression by hybridization to cDNA probes. Again, no PCR-mediated methods are described.

Furthermore, and with respect to claims 13-15, Erlander et al. do not disclose the use of a detectable nucleic acid molecule which comprises a T7 promoter. The reliance on page 4, lines 12-13, page 12, lines 3-13 and 15-27, and page 13, lines 1-8, is misplaced. These passages are the content of Examples 3 and 4 which are part of the microarray based methods disclosed by Erlander et al. Examples 3 and 4 relate to RNA amplification using a T7 promoter based system to 1) generate the initial cDNA for *in vitro* transcription of RNA and 2) to produce additional RNA for conversion into cDNA. The resultant cDNA, which the statement of the rejection appears to assume as comprising a T7 promoter, is not disclosed as used as a probe. Instead, Erlander et al. provide Example 6 (pages 13-14) which describes the labeling of cDNA probes with fluorescent Cy3 dye which probes are hybridized to cDNAs on a microarray. The individual cDNAs on the microarray are not "a ligand in a cell or tissue sample" as required by claim 1. As the Examiner will no doubt appreciate, cells and tissues samples do not contain cDNAs. Accordingly, it is not possible for the microarray based methods to anticipate the instant claims.

In light of the foregoing, Erlander et al. simply do not disclose the instant invention. Accordingly, no *prima facie* case of anticipation has been presented, and this rejection may be properly withdrawn.

Claims 1-4, 6-12, and 19-20 were rejected under 35 USC § 102(e) as allegedly anticipated by Bova (USP 6,040,139).

Applicants have carefully reviewed the statement of the instant rejection and respectfully traverse because no *prima facie* case of anticipation is present. Simply put, Bova does not teach all the requirements of the claims.

Specifically, Applicants note that the instant rejection asserts that Bova teaches "a binding agent (antibody), which binds to said ligand (nucleic acid) wherein said agent is attached to a detectable nucleic acid molecule (see column 16, lines 60-67, column 17, lines 1-5, column 12, lines 64-67, and column 13, lines 1-35". Applicants have carefully reviewed those passages and respectfully submit that Bova fails to disclose any antibody that is bound or attached to a nucleic acid molecule of any type.

Column 16, lines 60-67, describe the use of "monoclonal mouse anti-human leucocyte common antigen (DAKO-LCA) and monoclonal mouse anti-human monocyte/macrophage CD68 (DAKO-CD68)" which would bind two human proteins (LCA and CD68, respectively) rather than a nucleic acid molecule as asserted in the instant rejection. There is also no indication of either of these antibodies being attached to a detectable nucleic acid molecule as required by the claims.

Column 17, lines 1-5, describe the use of goat anti-mouse secondary antibodies linked to Cy3 (a very stable fluorescent dye). These secondary antibodies bind the LCA and CD68 binding antibodies described above. So these secondary antibodies also do not bind a detectable nucleic acid molecule. The Cy3 dye is also not a detectable nucleic acid molecule.

Column 12, line 64, through column 13, line 35, also fail to describe any antibody with an attached nucleic acid molecule. Contrary to the allegation in the instant rejection, this passage describes the antibodies used in the Bova disclosure as being directed to particular protein epitopes such that they can be used to identify cells containing the epitopes such that the non-identified cells can be ablated. The specific example (column 13, lines 4-17) describes use of an antibody which binds PSA to identify PSA containing cells followed by staining of all prostate epithelial cells. The staining is described as being possibly performed with "propidium iodide which selectively stains DNA." (see column 13, lines 29-30). The antibodies do not bind

nucleic acid molecules and are not attached to nucleic acid molecules. The antibodies are not even attached to the propidium iodide.

To the contrary, column 13, lines 30-35, describe the antibodies as optionally bound to a variety of labels, none of which are nucleic acid molecules.

Moreover, and with respect to claim 4, Bova does not disclose any PCR reaction related to a nucleic acid molecule attached to a binding agent. The fact that Bova fails to disclose a binding agent (antibody) attached to a nucleic acid molecule is explained above. The fact that the binding agents (antibodies) do not bind nucleic acid molecules has also been explained above. Accordingly, Bova cannot anticipate claim 4.

In light of the foregoing, Bova simply does not disclose the instant invention. Accordingly, no *prima facie* case of anticipation has been presented, and this rejection may be properly withdrawn.

Claims 1, 3-4, 6 and 19 were rejected under 35 USC § 102(b) as allegedly anticipated by Gracia et al.

Applicants have carefully reviewed the statement of the instant rejection and respectfully traverse because no *prima facie* case of anticipation is present. Simply put, Gracia et al. do not teach all the requirements of the claims.

Specifically, Applicants note that the instant rejection relies upon the methods described on page 599, right column of Gracia et al. The rejection asserts that passage as teaching "a binding agent (biotinylated cDNA)". But Applicants have carefully reviewed the passage and respectfully point out that the labeled cDNA described therein was prepared by a PCR reaction with use of biotin-16-dUTP, which would result in a cDNA labeled with biotin throughout its sequence (at positions where dUTP would have been incorporated). As such, where is the binding agent attached to a detectable nucleic acid molecule as required by claim 1? Stated differently, the resultant cDNA, which is used in its entirety as an agent which hybridizes (binds) to samples on untreated slides, *is not* attached to a separate detectable nucleic acid molecule as required by the claims.

Given the absence of a detectable nucleic acid molecule attached to a binding agent, Gracia et al. cannot disclose any PCR reaction of such a nucleic acid molecule as required by claim 4. Accordingly, Gracia et al. cannot anticipate claim 4.

As such, Gracia et al. simply do not disclose the instant invention. Accordingly, no *prima facie* case of anticipation has been presented, and this rejection may be properly withdrawn.

Claims 1-3, 6, 16-17 and 19 were rejected under 35 USC § 102(a) as allegedly anticipated by Englert et al.

Applicants have carefully reviewed the statement of the instant rejection and respectfully traverse because no *prima facie* case of anticipation is present. Simply put, Englert et al. do not teach all the requirements of the claims.

Specifically, Applicants note that the instant rejection relies upon the "Capture of POV1 (PB39) cDNA" methods described on pages 1527 and 1529 as well as Figure 3 (page 1528). None of these passages, however, describe the instant invention. Contrary to the statement of the instant rejection, the ^{33}P-labeled POV1 and β-actin cDNAs produced by PCR are not contacted with "a ligand in a cell or tissue sample" as required by claim 1. To the contrary, the POV1 cDNA was contacted with "a plasmid containing the entire POV1 cDNA" as shown in Figure 3 and discussed on page 1529. The β-actin cDNA was only contacted with the 10 capture layers through which the cDNA passed without binding (hybridization).

Moreover, and contrary to the assertion in the instant rejection, Englert et al. fail to disclose capturing or isolating of cells of interest as required by claim 1. Claim 1 requires the staining of a sample to identify cells of interest which are then captured or isolated. Figure 1 and the left column of page 1528 do not meet this requirement because the cells alleged to be captured by (transferred to) the layers are not from a sample that has been stained. Page 1528, left column, lines 5-9, describe the use of ECL after transfer (capture) of tissue on the layers. Page 1257, right column, and Figure 2 (page 1528) of Englert et al. describe the capture layers as being coupled to individual antibodies. None of these antibodies are attached to a detectable

nucleic acid molecule. Neither are any of the antibodies described as binding any nucleic molecule.

In light of the foregoing, Englert et al. simply do not disclose the instant invention. Accordingly, no *prima facie* case of anticipation has been presented, and this rejection may be properly withdrawn.

Claims 1, 3-7, and 18-19 were rejected under 35 USC § 102(a) as allegedly anticipated by Ehrig et al.

Applicants have carefully reviewed the statement of the instant rejection and respectfully traverse because no *prima facie* case of anticipation is present. Simply put, Ehrig et al. do not teach all the requirements of the claims.

Specifically, Applicants note that the instant rejection relies upon the use of nucleic acid binding dyes (as the binding agent) used to stain DNA (as the ligand) in samples. As explained above, the instant claims require the binding agent to be attach to a detectable nucleic acid molecule, which molecule is distinct from the ligand being detected. Ehrig et al. discloses no dye attached to a detectable nucleic acid molecule as required by the claims. Accordingly, Ehrig et al. cannot anticipate the claims.

Given the absence of a detectable nucleic acid molecule attached to a binding agent, Ehrig et al. cannot disclose any PCR reaction of such a nucleic acid molecule as required by claims 4, 5 and 18. Accordingly, Gracia et al. cannot anticipate these claims.

As such, Ehrig et al. simply do not disclose the instant invention. Accordingly, no *prima facie* case of anticipation has been presented, and this rejection may be properly withdrawn.

CONCLUSION

In light of the above amendments and arguments, Applicants respectfully submit that claims 1-21 are in condition for allowance and respectfully urge earlier indication to this effect with passage of the application to issue.

With respect to the amendments to claim 1, Applicants point out that they are mere changes of expression as addressed by Hubbell v. U.S.[1]

If the Examiner believes a telephonic discussion would expedite prosecution of this application, he is encouraged to telephone the undersigned at the number provided below.

Respectfully submitted,

Kawai Lau, Ph.D.
Reg. No. 44,461

TOWNSEND and TOWNSEND and CREW LLP
Two Embarcadero Center, Eighth Floor
San Francisco, California 94111-3834
Tel: 858-350-6100
Fax: 415-576-0300
Attachments
KL:ps
60293391 v1

[1] 179 U.S. 77, 80; 21 S. Ct. 24, 25; 45 L. Ed. 95, 98; 1900.